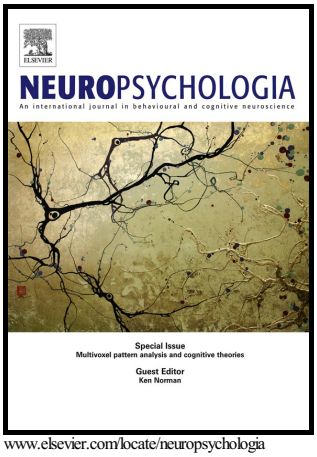

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Hemispheric contributions to language reorganisation: An MEG study of neuroplasticity in chronic post stroke aphasia

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Abstract

Previous studies have demonstrated that efficient neurorehabilitation in post stroke aphasia leads to clinical language improvements and promotes neuroplasticity. Brain areas frequently implicated in functional restitution of language after stroke comprise perilesional sites in the left hemisphere and homotopic regions in the right hemisphere. However, the neuronal mechanisms underlying therapy-induced language restitution are still largely unclear. In this study, magnetoencephalography was used to investigate neurophysiological changes in a group of chronic aphasia patients who underwent intensive language action therapy (ILAT), also known as constraint-induced aphasia therapy (CIAT). Before and immediately after ILAT, patients' language and communication skills were assessed and their brain responses were recorded during a lexical magnetic mismatch negativity (MMNm) paradigm, presenting familiar spoken words and meaningless pseudowords. After the two-week therapy interval, patients showed significant clinical improvements of language and communication skills. Spatio-temporal dynamics of neuronal changes revealed a significant increase in word-specific neuro-magnetic MMNm activation around 200 ms after stimulus identification points. This enhanced brain response occurred specifically for words and was most pronounced over perilesional areas in the left hemisphere. Therapy-related changes in neuromagnetic activation for words in both hemispheres significantly correlated with performance on a clinical language test. The findings indicate that functional recovery of language in chronic post stroke aphasia is associated with neuroplastic changes in both cerebral hemispheres, with stronger left-hemispheric contribution during automatic stages of language processing.

1. Introduction

More precise knowledge about neuronal processes accompanying language restitution and functional recovery is needed to develop more effective treatment procedures for patients suffering from aphasia. This is of utmost importance as post stroke aphasia (PSA) affects approximately 30-40 % of all stroke sufferers worldwide and often leads to chronic and debilitating cognitive impairments (Pedersen et al., 1995; Berthier, 2005; Engelter et al., 2006) which has a detrimental effect on the quality of life of patients and their carers. The neurophysiological mechanisms underlying functional restitution of language in PSA are still not fully understood. In PSA, perisylvian language regions in the language-dominant left hemisphere (LH) are usually affected, causing damage to the core language network and resulting in difficulties in nearly all domains of language processing. In this research context, one of the key questions is whether homotopic areas in the unaffected right hemisphere (RH) or perilesional regions in the impaired left hemisphere play a crucial role in neuroplasticity and in the reorganisation of the brain's language system.

Research on the restitution of language functions in chronic aphasia has led to inconsistent findings with regards to the role of the left and right cerebral hemispheres in functional recovery after stroke. Neuroimaging studies in the healthy brain have demonstrated that cortical regions in both hemispheres are involved when processing language: Whereas Broca's area in the inferior frontal gyrus of the left hemisphere seems to be involved in syntactic, semantic and phonological processing (Price, 2000; Bookheimer, 2002; Saur et al., 2008), lexico-semantic activation for processing different word categories has been found in perisylvian language areas of the LH as well as bilaterally in sensory and - motor areas, including premotor, motor and visual areas (Pulvermüller et al., 2009). Thus, it seems obvious that language recovery is either supported by (partially) preserved neuronal pathways in perilesional areas in the

damaged LH and/or by recruitment of brain regions in the intact RH which may already be part of the semantic language network.

As mentioned above, research on neuronal plasticity in aphasia has led to controversial findings. While the majority of studies demonstrated LH perilesional involvement (Heiss et al., 1999; Price and Crinion, 2005; Breier et al., 2007; Marcotte et al., 2012; MacGregor et al., 2015) in language recovery, others reported recruitment of RH regions, particularly in the inferior frontal lobe (Basso et al., 1989; Weiller et al., 1995; Basso and Macis, 2011; Mohr et al., 2014) or even involvement of both hemispheres (Pulvermüller et al., 2005). Interestingly, the activation dynamics and functional lateralisation patterns during language recovery seem to depend on a range of different variables, for example on the efficacy of neurorehabilitation or the recovery phase (Thomas et al., 1997; Saur et al., 2006). Moreover, several neuroimaging studies have shown correlations between (clinical) language functions and brain activation patterns in LH language areas in patients with PSA (Pulvermüller et al., 2005; Breier et al., 2006; Heiss and Thiel, 2006; Meinzer et al., 2008), indicating the importance of recruitment of language networks in the left hemisphere for the functional recovery of language and communication abilities.

Based on these findings, it seems most promising to investigate brain reorganisation and therapy-induced changes in chronic post-stroke aphasia as a result of speech and language therapy that yields rapid significant improvements. In this case, any neurofunctional changes observed cannot be attributed to spontaneous restitution or to changes in mood, social situation or other factors emerging slowly over time. Constraint-induced aphasia therapy (CIAT, Pulvermüller et al., 2001), also called intensive language action therapy (ILAT, Berthier and Pulvermüller, 2011; Difrancesco et al., 2012) is a short-term intensive therapy for PSA patients with varying degrees of symptom severity. The efficacy of ILAT in the treatment of chronic and sub-acute aphasia has been demonstrated by a number of randomised controlled clinical trials

(RCTs; Pulvermüller et al., 2001; Meinzer et al., 2005; Maher et al., 2006; Berthier et al., 2009, Sickert et al., 2014). Within two weeks of intensive application, this method leads to reliable improvements of language and communicative skills in patients with post-stroke aphasia.

The core therapeutic elements of ILAT are: treatment intensity, the practise of language in the context of actions and the use of spoken language in daily-life communicative situations. In ILAT, patients are encouraged to use their remaining verbal communication skills in order to practise communicative speech acts such as "planning an action" or "making a request" in the context of "language action games" (for more details on methodological aspects of this therapy see Difrancesco et al., 2012). In accordance with the method used in constraint-induced movement therapy (Taub et al., 2002; Pulvermüller and Berthier, 2008; Pulvermüller et al., 2015), ILAT is practised in a high intensity fashion for several hours per day.

A number of studies have looked at ILAT -induced changes in brain activation and cortical reorganisation in chronic PSA patients, however, the findings are inconsistent with regards to hemispheric contribution to language recovery. Evidence for recruitment of perilesional areas in the left hemisphere were reported by Meinzer et al. (2008) who found an increase in fMRI-BOLD activation accompanied by improvements of overt naming for repeatedly practiced items. Activation changes in the LH were also reported in an MEG study indicating successful lexical differentiation only 50 ms after stimulus identification, which became apparent after therapy (MacGregor et al., 2015). Employing a language comprehension task using MEG before and after ILAT, Breier and co-authors (2009) suggested that perilesional areas in the LH may be important for stable language improvements after therapy.

In contrast, other evidence indicates that successful language recovery after ILAT is associated with an increase in BOLD activation in both hemispheres in an overt naming task (Kurland et al., 2012). This bilateral involvement in language restitution is in line with previous data from a lexical decision paradigm, which demonstrated an enhancement of brain activity

over both hemispheres using electroencephalography (EEG, Pulvermüller et al., 2005). In the latter study, an increase of word-specific brain activation over both hemispheres was positively correlated with clinical language improvements after ILAT in chronic aphasia patients. Furthermore, other studies reported ILAT-related brain reorganisation in fronto-temporal areas of the RH (Mohr et al., 2014) employing an auditory semantic ambiguity task using fMRI. Moreover, a positive correlation of language improvement after ILAT with greater relative pre-therapy brain activation in the RH was reported (Breier et al., 2006; Richter et al., 2008).

Thus, neuroimaging data on therapy-induced changes after ILAT demonstrate contributions of both hemispheres in functional recovery. The inconsistencies in laterality data across studies might be attributed to differences in neuroimaging methods, language tasks and patient characteristics. It is therefore necessary to systematically investigate the influence of each of these factors on neuroplasticity.

Magnetoencephalography (MEG) is a particularly useful method for detecting neuronal activity during language processing as it provides high temporal and high spatial resolution and is a very patient-friendly recording method. MEG can track changes in brain activity within the millisecond time range and its use is therefore optimal for studying language processes which are generally characterised by very fast temporal dynamics. One of the best-established paradigms in electro-and magnetoencephalography is the *lexical mismatch negativity (MMN)* design, which uses a passive listening task (Pulvermüller et al., 2001; Shtyrov & Pulvermüller, 2007) and allows the recording of event-related brain potentials in response to infrequent (deviant or oddball) acoustic lexical stimuli randomly presented in a context of frequent (standard lexical) stimuli (Näätänen & Alho, 1995; Näätänen, 2001; Näätänen et al., 2007). A great advantage of the MMN paradigm is its independence from focussed attention, which is frequently compromised in neurological patients. Hence, the MMN is considered to represent a brain correlate of automatic cognitive processing of auditory information and is often assigned a great

potential in clinical research as it can provide an index of various cognitive dysfunctions, language deficits included (Näätänen et al., 2012; 2014).

Lexical MMN data in healthy individuals have demonstrated enhanced amplitudes for meaningful words compared to meaningless pseudowords (Pulvermüller et al., 2001; Endrass et al., 2004; Pettigrew et al., 2004; Pulvermüller et al., 2004) with lexical differentiation occurring around 100-200 ms after the word recognition point (Shtyrov et al., 2005; 2012). This enhanced lexical MMN response is typically explained by a strong automatic activation of neural memory traces for real words that are underpinned by robust connections within the networks of neurons of which they are formed (Pulvermüller et al., 2001).

Functional lateralisation towards the language-dominant left hemisphere has been reported in a number of neurolinguistic MMN studies. These used separate phonemes and consonant- vowel (CV) syllables in healthy participants, indicating left-hemispheric dominance in phonological speech processing already at a pre-attentive processing level (Näätänen et al., 1997; Alho et al., 1998; Shtyrov et al., 1998), and, more importantly, lexical stimuli (e.g. nouns and verbs) that indicated left-lateralised automatic word processing as indexed by early MMN dynamics in left temporal-frontal cortices (Pulvermüller et al., 2006; Pulvermüller & Shtyrov, 2009).

MMN research in patients with aphasia has revealed reduced MMN responses to CV sounds, but mostly unimpaired MMN responses to pure tone deviants when compared to healthy matched controls (Aaltonen et al., 1993; Wertz et al., 1998; Csepe et al., 2001; Ilvonen et al., 2003; 2004). In contrast, reduced lateralisation of MMN amplitudes in aphasics compared to controls has been reported (Breier et al., 2007), or, in fact, even larger MMN activity over the right hemisphere (Teki et al., 2013), again demonstrating inconsistencies in functional lateralisation patterns.

In order to address the apparent controversies in the field and to assess the role of LH vs. RH circuits in language restitution processes in PSA, we set out to investigate the neuronal changes induced by ILAT, and more specifically, to measure spatio-temporal patterns of MMNm-related automatic language processing employing an auditory lexical MMNm paradigm in a group of chronic aphasia patients. We were particularly interested in functional neuronal changes underlying language recovery and the suitability of the MMNm design to map therapy-induced cortical changes. As we focussed on MMNm specific activation patterns, we predicted changes in neuromagnetic activation following ILAT treatment around 200 ms after stimulus recognition. In line with previous data (Pulvermüller et al., 2005, MacGregor et al., 2014), we expected to find an increased MMNm activation after therapy, specifically for words, but not for pseudowords. Another focus was on studying the pattern of laterality of such word-related enhancement of the MMNm brain response.

2. Material and methods

2.1. Patients

Fourteen patients with chronic (> one year post-stroke) aphasia underwent two weeks of ILAT. All patients (5 females, mean age: 56.9 years) presented with language impairments following a single stroke affecting the territory of the left middle cerebral artery and resulting in non-fluent Broca's aphasia with different degrees of severity. Information on lesion location was obtained by medical records and/or structural magnetic resonance imaging (MRI) or computer tomography (CT) scans where available. In all patients, lesions were of medium to large size and involved the left-perisylvian language cortex including, to different degrees, the frontal, temporal, insular and parietal cortices and underlying subcortical structures (internal capsule, deep white matter). None of the patients had a lesion in the right hemisphere. Only patients who

were native monolingual speakers of English before stroke were included. All patients had normal hearing, as assessed by measuring hearing threshold before experimental testing. Handedness was evaluated with the Edinburgh Handedness Inventory (Oldfield, 1971). Only right-handed patients (before stroke) and patients with no additional neurological or psychiatric diagnosis were included in the study. Socio-demographic and clinical data of all patients are provided in *Table 1*. All patients had obtained conventional speech and language therapy after stroke, but did not participate in any additional language therapy other than ILAT during the course of the study. Inclusion criteria were assessed at a pre-screening appointment where detailed study information was provided. Patients were informed verbally and were also provided with a visual timeline of the study protocol. All 14 patients completed the two-week ILAT protocol and clinical language pre-post evaluation. Twelve patients volunteered to participate in the MEG-MMNm study. Some data from this group of patients were previously published (MacGregor et al., 2015). In contrast to our present study, this previous study explored ultra-rapid (< 100ms) neuromagnetic brain responses. What we report in the present study, is a new and independent analysis, specifically focussing on activation changes in lexical MMNm as a neurophysiological marker of improved language processing. Moreover, we were interested in correlations of a wider range of clinical-behavioural measures of language improvements than we used previously. Patients gave written informed consent before entering the study. Patients were recruited via local self-help groups in the Cambridgeshire (UK) area and ethical approval was obtained from Cambridgeshire Local NHS Research Ethics Committee (NRES).

Table 1. Clinical and demographic data of 14 patients who engaged in two weeks of ILAT. Patients were diagnosed with Broca's aphasia resulting from a single CVA affecting the middle cerebral artery. Patients 3 and 4 did not participate in MEG testing.

Patient	Sex	Age	Time poststroke (years)	Handedness (laterality score)	Aetiology	Cortex Lesion location	Aphasia severity
1	F	40	2.2	R (100)	Haemorrhage	Fronto-temporal	mild
2	F	73	1.8	R (100)	Ischemia	Fronto-temporal	moderate
3	M	65	6.7	R (100)	Ischemia	Fronto-temporal, parietal	residual
4	M	74	10.6	R (90)	Ischemia	Fronto-temporal	moderate
5	F	40	1.6	R (90)	Haemorrhage	Fronto-temporal	moderate
6	M	69	2.1	R (100)	Ischemia	Fronto-temporal	moderate
7	M	48	1.4	R (90)	Ischemia	Fronto-temporal	severe
8	M	72	2.7	R (70)	Ischemia	Fronto-temporal	severe
9	F	60	11.4	R (80)	Ischemia	Fronto-temporal	mild
10	F	26	13.8	R (100)	Haemorrhage	Fronto-temporal, parietal	residual
11	M	41	1.6	R (90)	Ischemia	Fronto-temporal	severe
12	M	76	19.5	R (80)	Haemorrhage	Fronto-temporal	mild
13	M	54	1.7	R (100)	Ischemia	Fronto-temporal, parietal	severe
14	M	59	8.7	R (100)	Ischemia	Fronto-temporal	moderate
Mean (SD)		56.93 (15.78)	6.13 (5.8)	92.14 (9.75)			

2.2. Intensive language action therapy

All patients participated in and completed intensive language action therapy for two consecutive weeks. ILAT was administered on weekdays for 3-4 hours per day. Treatment was delivered in a group setting with three patients and two therapists. Language games were practised with the help of card sets differing in complexity, difficulty and communicative purpose (e.g. making a request or planning an action). Verbal communication and language skills were practised in a behaviourally relevant context (for more details see Pulvermüller et al., 2001;

Difrancesco et al., 2012). Patients were discouraged from using nonverbal communication (e.g. gestures) unless accompanied by the simultaneous use of spoken language.

2.3. Clinical language assessment

Clinical language testing took place before and immediately after the therapy and included the following tests: Boston Diagnostic Aphasia Examination (BDAE, Goodglass and Kaplan, 1972), subtests Auditory Comprehension, Syntactic Processing and the Boston Naming Test. In addition, the Token Test (TT, De Renzi and Vignolo, 1962) and the Communicative Aphasia Log (CAL, Pulvermüller et al., 2001) were applied. The BDAE and TT are standardized and widely used clinical tests for the assessment of aphasia symptoms. Auditory comprehension was assessed with the BDAE subtests "Word comprehension by categories" (max. score: 30) and "Semantic probe" (max. score: 60). Overall auditory comprehension scores were calculated by adding up correctly identified items in both subscales (max. overall score: 90). The TT also assesses auditory comprehension and (to some degree), verbal memory (De Renzi and Vignolo, 1962). Here, patients have to follow commands and perform actions by pointing to and manipulating tokens differing in shape and colour (max. error score: 50).

Syntactic processing was assessed with the BDAE subtests "Touching A with B" (max. score: 12), "Reversible possessives" (max. score: 10) and "Embedded sentences" (max. score: 10). Again, overall syntactic performance was determined by adding up scores from the three subtests (max. overall score: 32).

Naming ability was tested with the standard version of the Boston Naming Test (BNT, max. score: 60).

The CAL is a questionnaire used to assess the amount and the quality of everyday communication on a 6-point-Likert scale. The CAL contains 18 items each for the category "amount of communication" and "quality of communication" (max. score: 90 for each

communication category). There are two versions of this test, one version for patients' self-evaluation and one version for the evaluation by carers or therapists. In our study, one version was filled out by patients, the other by patients' carers. Pre- and post therapy data on all these tests (overall scores) are provided in *Table 3*.

2.4. MMN study

2.4.1. Stimuli

Stimuli were monosyllabic words and acoustically-similar pseudowords. Two stimulus sets were created comprising spoken words and pseudowords, which had previously been shown to elicit robust lexicality effects in neuromagnetic brain responses in healthy participants (Shtyrov & Pulvermüller, 2002; Garagnani et al., 2009; Shtyrov et al., 2010). Each stimulus set consisted of one standard stimulus with a consonant-vowel (CV) structure (*[baj], [paj]*) and two deviant lexical stimuli, created by adding a final unvoiced stop consonant [p] or [t] to the standard stimulus to produce a real word (*bite, pipe*) or a meaningless pseudoword *([bajp],[pajt]*). Variations of the factor *Lexicality* (word versus pseudoword) and acoustic-phonetic features of the stimuli were performed using an orthogonal design, in which the same sounds ([p], [t]) were presented in a word as well as in a pseudoword context (see *Table 2*). This ensured that differences in brain responses could be attributed to the experimental variables of *Lexicality* and *Session* (pre versus post therapy), ruling out any confounding factors associated with acoustic or phonetic features of the respective stimuli.

Table 2. MMN design: Orthogonal variation of lexicality (words versus pseudowords) and acoustic-phonetic features (Coda: [p] or [t]) across the two sets of stimuli. Each set comprised a standard CV syllable, a **word deviant** (in bold) and a pseudoword deviant.

MMN Condition (overall percentage of stimuli)	Stimulus Set I	Stimulus Set II
Standard Consonant Vowel (CV) syllables (83.3%)	*[baj]*	*[paj]*
Deviant [*p*] (8.3%)	*[bajp]*	**[pajp] "pipe"**
Deviant [*t*] (8.3%)	**[bajt] "bite"**	*[pajt]*

Careful procedures were followed to ensure that words and pseudowords in the two sets were orthogonalised for physical acoustic features and could be recognised at exactly the same point in time. Multiple examples of the items were spoken in a randomised order by a female native speaker of British English, and digitally recorded (sampling rate 44.1 KHz). The standard stimuli ([*baj*] and [*paj*]*)*, one for each set, were created by choosing exemplars of the deviants where the syllable-final phonemes ([p], [t]) had been extracted. The standards had the same fundamental frequency or F0 (272 Hz), and were adjusted to have equal duration (330 ms) and average sound energy or root-mean-square (RMS) power. The selected exemplars of the critical syllable-final phonemes [p] and [t] had the same duration (80 ms) and were also normalised to match for average RMS power. These phonemes were cross-spliced onto each of the standard stimuli to produce the four deviant stimuli. Thus, different co-articulation cues could be avoided and acoustic differences between stimuli were kept to a minimum. The silent closure time between the consonant vowel end of the standard stimulus and onset of the plosion of the final stop consonant in the deviants was adjusted to identical duration (80 ms). Thus, the onset of the final stop consonant in the deviants ([t] or [p]) was the first point in time where the standards differed from the deviants, as well as the earliest point in time at which the perceptual differentiation between words or pseudowords was possible. We therefore time-locked neural responses to this point as it was the earliest point in time at which the lexical MMN response could be triggered. This careful stimulus selection ensured that the standard-deviant acoustic contrast, the critical stimulus feature generating the MMN, was identical across conditions and most importantly, identical in word and pseudoword conditions. Thus, any differences in MMNs between the two main stimulus types could only be due to their lexical status.

Figure 1 presents waveforms of example standard and deviant stimuli with respective duration and phonetic representations (formants) time locked to MEG epoch durations relative to the stimulus.

Figure 1 here

2.4.2. Procedure

Twelve of the fourteen patients took part in the MEG study. Two MEG recordings were carried out with each patient: the day before commencement of the treatment and one day after termination of the therapy. In both testing sessions (below referred to as pre- and post-therapy or Sessions 1 and 2, respectively), patients were seated in a dimly-lit and magnetically shielded room (IMEDCO GMBH, Switzerland). They were instructed to attend to a silent nature film and to ignore any incoming acoustic stimuli. Standards and deviants were presented binaurally at a comfortable hearing level through plastic tubes attached to in-ear headphones (ER3A insert earphones, Etymotic Research, Inc., IL, USA). Hearing threshold was determined for each patient with pure tones of 1000 Hz to ensure that they could hear equally (within 10 dB) in both ears. Normal hearing thresholds were found for all patients.

The two stimulus sets were presented in separate blocks with counterbalanced order of presentation across participants. Each block contained 810 standards and 80 of each deviant, thus combined deviant probability was 16.5 % in each block. Presentation order of standards and deviants was randomised. It was ensured that a deviant stimulus would have to be followed by at least one standard stimulus and never by another deviant item. Additional 10 standard stimuli were presented at the start of each block to establish the standard sequence. Stimuli were presented with a mean stimulus onset asynchrony (SOA) of 900 ms (jittered by ±20 ms in 10 ms steps) using E-Prime 2.0 software (Psychology Software Tools, Inc., Pittsburgh, PA, USA).

2.4.3. MEG Recording

MEG was continuously recorded using a sampling rate of 1000 Hz and a bandpass filter from 0.03 to 330 Hz). Signals were recorded by a whole-head Vectorview system (Elekta

Neuromag, Helsinki, Finland) with 204 planar gradiometer and 102 magnetometer sensors. Head position relative to the sensor array was continuously recorded by five Head-Position Indicator (HPI) coils which emitted sinusoidal currents (293-321 Hz). Before MEG recording, positions of the HPI coils relative to three anatomical points (nasion, left and right pre-auricular points) were digitally determined by a 3-D digitiser (Fastrak Polhemus, Colchester, VA). To monitor eye movements, vertical and horizontal electro-oculograms (EOGs) were recorded continuously.

2.4.4. MEG Data Processing

Data from all 306 sensors were processed using the temporal extension of the signal-space separation technique (tSSS) in order to keep the contribution of magnetic sources from outside the head to a minimum and to reduce any within-sensor artifacts (Taulu & Kajola, 2005). This was done by using MaxFilter 2.0.21 software (Elekta Neuromag) where any correlates of MEG signal originating from external sources were removed; additionally, compensation was made for within-block head movements as measured by HPI coils enabling data realignment to the same spatial coordinates across blocks. Data were subsequently processed using MNE Suite Software (version 2.7.3, Martinos Center for Biomedical Imaging, Charlestown, MA, USA) and Matlab 2009 (MathWorks, Natick, MA, USA).

Continuous data were epoched between -50 ms and 600 ms relative to the onset of the stimulus-final plosion for the deviants or corresponding silent period for the standards, baseline-corrected over the 50 ms pre-trigger period, and bandpass-filtered between 1 and 30 Hz. We selected baseline duration of 50 ms for the following reason: A contrast between shorter stems as standards and longer stem + plosion as deviants was used to elicit MMN. The relevant acoustic contrast was placed at the stimulus point (*divergence point, DP)* that the relevant psycholinguistic processes could be time-locked to, indicating the need to correct the baseline before the DP to minimize any drift- and noise-related effects. Word-final English plosive

consonants of the type used in the present study are usually preceded by a silent closure of 50-80 ms. Thus, a pre-divergence point baseline should ideally fall in this quiet period when no acoustic stimulation is present. A longer baseline would have made it overlap with the voiced part of the stem, increasing noise in the baseline. As a the next analysis step, epochs were rejected when the magnetic field variation at any gradiometer or magnetometer exceeded 2000 fT/cm or 3500 fT respectively, or when voltage variation at either bipolar EOG electrode exceeded 150 µV. For each individual patient, average event-related magnetic fields (ERF) were computed for each stimulus and MMNm was calculated by subtracting the standard response from respective deviants. Separate averages were then calculated for words and pseudowords in the pre and post therapy session. In each of the 102 planar gradiometer pairs, ERFs were quantified as the absolute amplitude of the vector sum of the signal subcomponents in the two orthogonally oriented gradiometers in each pair following the formula:

$$MMN\ for\ each\ gradiometer\ pair = \sqrt{MMN\ grad\ 1^2 + MMN\ grad\ 2^2}$$

Twelve gradiometer channels (3 pairs over each hemisphere) positioned over fronto-temporal brain areas were selected as regions of interest as they showed the largest MMNm signals (over the left hemisphere) in the typical MMN time window (100-200 ms post stimulus onset). These gradiometer pairs were used in all subsequent statistical analyses.

Sensors and time windows were selected as follows: Average RMS time courses were computed across all conditions, sessions and sensors and visually inspected to find sensors with maximal responses for the MMNm response (deviant minus standard). Subsequently, three sensors were selected which were located over left fronto-temporal regions, as expected from previous studies. For comparison, and to test for laterality effects, three additional homologous sensors in the right hemisphere were selected. After visual inspection, four pronounced response peaks were selected: 80-100 ms, 170-210 ms, 235-275 ms and 280-320 ms.

For analysis, event-related magnetic field gradients elicited in response to the standard and deviant stimuli (words and pseudowords) for pre- and post-therapy sessions were calculated. Data were averaged over the fronto-temporal gradiometer pairs (in both hemispheres) which were later included in the statistical analyses. The time course of ERFs of standard and deviant responses for words and pseudowords before and after therapy is displayed in *Figure 2*. The MMNm time window (170-210 ms) in which significant changes in activation were expected is highlighted. Predictions were only made with respect to the MMNm time window.

Source localization analysis in our patient group was not pursued, because some requirements of realistic modelling could not be met by the present study. Proper distributed source estimates were not easily possible given that they require higher signal-to-noise ratios (SNRs) (Hämäläinen & Ilmoniemi, 1994; Gramfort et al., 2014) than typically available in neurological patient data. Furthermore, structural MRIs, required to restrict the source space, could not be obtained for the full patient group due to safety constraints. Moreover, equivalent current dipole (ECD) models, are suboptimal for language tasks, as neuronal activity does not originate from a single brain area, but from multiple sites (Dale et al., 2000; Pulvermüller et al., 2003; MacGregor et al., 2012). Therefore, as ECD changes in our patient sample might have incorrectly attributed changes in distribution of sources to their strength, statistical analysis was restricted to surface MEG fields recorded from the left and right hemisphere.

Figure 2 here

3. Results

3.1. Language assessment

In the statistical pre-/post-therapy analyses, only the twelve patients who participated in MEG recordings as well as in ILAT were included. Pre- and post-therapy scores from the *BDAE* subtests, the *Token Test* and the *CAL* were analysed using paired sample t-tests (*see Table 3*).

Statistically significant improvements of language functions after therapeutic intervention were found in the *BNT* [t (11) = 3.08, p = .01] and the *TT* [t (11) = 2.53, p = .028]. The subtest *Auditory Comprehension* of the *BDAE* showed only a marginally significant improvement after therapy [t (11) = 1.88, p = .09]. Quality of communication after therapy, as measured by the *CAL* was rated by patients to be significantly higher after therapy than before [t (11) = 2.86, p = .02]. Evaluation of communication by carers was obtained from 9 carers. Communication ratings by carers mirrored those obtained from patients, however, the effects were only marginally significant [t (8) = 2.07, p = .07]. A Pearson correlation showed a significant positive correlation (p <. 001) between *CAL* patients' ratings and carers' ratings.

Table 3. Mean (and standard deviation) pre- and post-therapy scores from subcategories of the Boston Diagnostic Aphasia Examination (BDAE): Auditory Comprehension, Syntactic Processing, and Boston Naming Test, and from the Token Test (TT), and the Communicative Activity Log (CAL). Higher scores in the BDAE indicate better performance. For the Token Test, errors are listed with lower scores indicating better performance. In the CAL, higher scores indicate better communication ratings. Differences between pre- and post-therapy scores were assessed with t-tests. Results are shown in the third column, with effect sizes (Cohen's d) and 95% Confidence Intervals. Statistically significant differences between pre- and post-therapy scores are highlighted in bold.

Test	Pre-therapy	Post-therapy	Pre-post comparison
BDAE Auditory Comprehension (max. 90)	84.10 (SD 0.67)	85.36 (SD 0.86)	p = .09 *(d=1.63)* *C.I. 0.7-2.4*
BDAE Syntactic Processing (max. 32)	18.79 (SD 1.44)	18.57 (SD1.70)	p =.48 *(d=-0.14)* *C.I. 0.88-0.6*
BDAE Boston Naming Test (max. 60)	28.58 (SD 12.40)	33.00 (SD 10.31)	**p = .01*** *(d=0.38)* *C.I. -0.36-1.13*
Token Test (max. errors: 50)	33.27 (SD 13.16)	26.22 (SD 8.87)	**p = .03*** *(d=0.62)* *C.I. -0.13-1.38*
CAL Patients' ratings amount (max. 90)	47.79 (SD 3.53)	51.14 (SD 3.95)	p = .17 *(d=0.89)* *C.I. 0.11-1.67*
CAL Patients' ratings quality (max. 90)	46.71 (SD 3.45)	54 (SD 3.95)	**p = .02*** *(d=1.96)* *C.I. 1.06-2.86*
CAL Relatives' ratings amount (max. 90)	52.67 (SD 4.74)	55.64 (SD 4.91)	p = .45 *(d=0.61)* *C.I. -0.14-1.37*
CAL Relatives' ratings quality (max. 90)	39.67 (SD 4.87)	46.71 (SD 8.13)	p = .07 *(d=1.05)* *C.I. 0.26-1.84*

3.2. MEG responses

Statistical analyses focused on the MMNm responses for words compared to pseudowords before and after ILAT in the left and right hemisphere.

Four time windows were selected (see above) and ANOVAs were calculated for each time window separately. Fronto-temporal sensor pairs were divided into three sensor locations (*anterior-medial-posterior*), the factor *Sensor Location* was used as a separate factor in subsequent ANOVAs to test for any activation differences with regards to the specific location of sensors over fronto-temporal brain areas. Additional factors used in the ANOVAs included *Lexicality* (words versus pseudowords), *Session* (pre versus post therapy) and *Hemisphere* (left versus right). Greenhouse-Geisser corrections were applied where appropriate.

The main focus of this study was on MMNm responses (amplitude increase for words after therapy in the typical MMN time window). As the predictions were focussed on one a priori defined deflection, there was no need for correction for multiple comparisons. Other time windows were only analysed ad-hoc solely for the purpose of completeness of analysis, but we did not have any a priori predictions about the outcome of these analyses.

Analysis of the first and earliest time window (80-100 ms) showed a main effect of *Sensor location* $F(2,22) = 4.09$, $p = .03$ with the highest activation at medial sensors compared to anterior and posterior ones

Most importantly, only the analysis of the second and standard MMNm time window (170-210 ms) revealed a significant three-way interaction of the factors *Session x Lexicality x Hemisphere* [$F(1,11) = 6.47$, $p = .027$], indicating significant differences in cortical activation between pre- and post- therapy sessions for words and pseudowords in both cerebral hemispheres (see *Figure 3*).

Figure 3 here

This three-way interaction was followed by separate ANOVAs within each stimulus category. Whereas no significant differences were obtained for pseudoword-evoked magnetic signals, analysis of word-evoked activity revealed a significant main effect of the factor *Session* with higher activation after therapy than at pre-therapy testing [F(1,11) = 6.92, p = .023: Pre-therapy: 9.007 fT/cm, Post-therapy: 11.836 fT/cm] and a significant two way interaction with the factors *Session x Hemisphere* [F(1,11) = 8.82, p = .013], reflecting hemispheric differences in pre-post changes observed for words. Post-hoc analyses carried out to follow this interaction showed that cortical activation for words over the language dominant LH was significantly larger after therapy than before [F (1,11) = 12.42, p = 005: Pre-therapy: 7.147 fT/cm, Post-therapy: 15.294 fT(cm), whereas no significant activation change was observed for the non-dominant RH. In addition, when analysing word responses in the post-therapy session only, a significant main effect of the factor *Hemisphere* was obtained [F(1,11) = 5.29, p = .042, LH: 15.294 fT/cm, RH: 8.379 fT/cm] further confirming significantly higher activation in the left than in the right hemisphere. Analysis of the word responses in the pre-therapy session revealed a main effect of the factor *Location* with highest activation in medial sensor locations [F (2,22) = 4.341, p = .044: Anterior: 0.731 fT/cm, Medial: 10.615 fT/cm, Posterior: 9.676 fT/cm].

Specific activation changes for words (but not pseudowords) after therapy were consistently observed over the left hemisphere for 10 (out of 12) patients. In order demonstrate that this activation change consistently occurred across individual patients, pre-post therapy laterality quotients were calculated on an individual subject basis using the formula

$$LQ = \frac{(LH - RH)}{(LH + RH)} \textbf{*100}$$

Laterality quotients for individual patients are presented in *Table 4.*

Table 4. Pre- and post-therapy laterality quotients based on ERF activity (fT/cm) calculated individually for each patient. Group means and medians for words and pseudowords, for pre- and post- therapy sessions are in bold. Positive numbers indicate left laterality.

Patient	Words		Pseudo words	
	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy
1	-26.44	- 5.39	35.13	83.66
2	-22.64	52.43	51.61	-61.19
5	-56.57	45.26	38.31	22.89
6	27.60	- 1.68	93.66	-43.71
7	-42.07	29.40	- 26.20	28.36
8	15.86	176.54	21.30	61.59
9	-37.19	- 61.8	42.09	- 29.97
10	-28.01	- 2.30	53.65	82.63
11	- 68.50	28.68	- 3.62	42.53
12	-27.69	- 22.90	-60.07	91.56
13	-76.16	11.67	-36.88	- 41.49
14	-100.31	43.15	-15.86	2.67
Mean	**- 36.84**	**24.42**	**16.16**	**19.51**
Median	**-32.60**	**20.17**	**28.21**	**25.62**

The time course and amplitudes of event-related magnetic field gradients of the MMNm responses (deviants minus standards) for pre- versus post-therapy session for words and pseudowords are presented in *Figure 4*.

Figure 4 here

Laterality quotients for words and pseudowords before and after the therapy were then submitted to a non-parametric Wilcoxon signed rank test. The results showed that LH laterality significantly increased over therapy (median values: -32.6 vs. 20.2, Z = -2.432, p = .015). These laterality effects are displayed in *Figure 5*, which displays topographical field gradient maps showing distribution of the MMNm responses to words for the pre- and post-therapy session over the left and right hemisphere.

Figure 5 here

Whereas analysis of the third time window (235-275ms) did not result in any significant main effects or interactions, analysis of the latest time window (280-320 ms) showed significant main effects of *Hemisphere* [F(1,11) = 7.71, p = .018; LH: 15.723 fT/cm; RH: 8.292 fT/cm] with stronger activation over the left than the right hemisphere and *Location* [F(2,22) = 5.25, p = .016; Anterior: 9.995 fT/cm; Medial: 14.408 fT/cm; Posterior: 11.620 fT/cm).

3.3. Correlations between clinical language tests and MEG responses

To further explore the association of clinical language changes after therapy with neurophysiological measures, Spearman Rank correlations between clinical language tests (changes in the TT and BNT) and changes in neuromagnetic activation (ERF amplitudes) in the left and right hemisphere for words and pseudowords were calculated for the time window 170-210 ms, as the relevant three-way-interaction was found here. Correlation analyses documented a relationship between behavioural and neurophysiological measures. More specifically, word-evoked changes in neuromagnetic activation over therapy significantly correlated with improvements in the Token Test after therapy. Reduced error rates in the TT correlated with an increase of word-specific brain activation in the LH (p= .045, r_s= - .59) after therapy. In the RH, a decreased error rate in the TT correlated with decreased brain activation for words after therapy (p = .0001; r_s = .88, see *Figure 6, supplementary materials)*. Correlation analysis between changes in BNT scores and neuromagnetic activation were non-significant. The data indicate that clinical improvements in language processing, particularly comprehension, were accompanied by therapy-induced neurophysiological changes in the left and right hemisphere.

4. Discussion

Changes in spatio-temporal MEG activation patterns after intensive language action therapy were measured in patients with chronic post stroke aphasia. Language processing before and after treatment was assessed by clinical language tests, communication scales and a lexical mismatch negativity task. The findings showed significant behavioural improvements in naming, auditory comprehension and in the quality of communication in everyday life situations after intervention. Furthermore, a therapy- related increase of MMNm amplitudes was observed over the left, language-dominant, hemisphere approximately 200 ms after words could first be recognised. This enhancement of cortical activation was present for meaningful words over fronto-temporal recording sites, but not for meaningless pseudowords. The findings confirm the effectiveness of ILAT in the treatment of chronic aphasia and demonstrate that the lexical MMNm is a valuable tool for detecting therapy-induced neurophysiological changes in language processing.

Robust clinical improvements after intensive language-action therapy have consistently and unanimously been reported in randomised controlled clinical trials as well as in other studies (Pulvermüller et al., 2001; Meinzer et al., 2005; Maher et al., 2006; Berthier et al., 2009; Sickert et al., 2014; Barbancho et al., 2015). The present data are in line with previous results and demonstrate improvements in a variety of language skills within only two weeks of treatment. More specifically, patients demonstrated improved language performance for naming, auditory comprehension, and quality of communication. As in previous studies, improved language skills were a result of intensive practice of pragmatic language use in so-called “language games” (Berthier and Pulvermüller, 2011; Difrancesco et al., 2012). Interestingly, although only pragmatic communication skills (e.g. making requests, planning activities) are explicitly practised in ILAT, other (non-pragmatic) language domains seem to benefit from this therapeutic

technique as well. For example, previously, patients consistently showed benefits in their naming abilities (Pulvermüller et al., 2001; Berthier et al., 2009; Meinzer et al., 2005; Mohr et al., 2014) and in auditory comprehension (Pulvermüller et al., 2001; Mohr et al., 2014). These findings suggest that ILAT has a positive impact on a range of specific language skills, thus affecting language at a more general abstract level, and therefore constitutes an effective short-term treatment for chronic and sub-acute aphasia.

All patients in our study were tested in the chronic stage of PSA (average duration of disease: 6.1 years) where spontaneous remission is very unlikely to occur (Berthier and Pulvermüller, 2011, Turkeltaub et al., 2011), particularly over such a short period of time (two weeks). Hence, any effects related to spontaneous remission are highly unlikely in our study and any changes observed after the two-week treatment interval can be attributed to language intervention. Moreover, since none of our patients engaged in any other speech and language therapy during the course of our study, gains in language skills can be related specifically to intervention with ILAT. Similarly, repetition effects per se cannot explain our data: if test repetition played an important role in our study, we would have expected to see significant pre-post changes in all BDAE subtests and in MMN pre-post changes to words and pseudowords. The fact that our findings showed specific activation changes only for words speaks against the influence of general repetition effects. Nevertheless, given that one of the short-comings of this study is the lack of a control group to monitor any task-related repetition effects or some other unspecific treatment effects, an influence of these factors can not entirely be ruled out.

It should be pointed out, however, that ILAT-specific benefits of language processing could be demonstrated in previous studies which did include patient control groups (Pulvermüller et al., 2001; Berthier et al., 2009). In addition, previous data have indicated stability of clinical and neuronal activation patterns across pre and - post testing sessions in aphasia patients as well as in healthy controls (Breier et al., 2009; Meinzer et al., 2005;

Barbancho et al., 2015). Thus, although the present results must be treated with caution, it seems rather unlikely that they can be solely attributed to repetition or unspecific treatment effects.

Neuromagnetic MEG responses demonstrated a significant increase in MMNm activity for words after treatment. This word-specific MMNm increase was only visible over the left hemisphere, whereas there was no significant activation change in the right hemisphere after therapy. As the MMN is an indicator of both automatic auditory change detection (Näätänen et al., 1997; 2007) and more importantly of automatic lexical processing (Pulvermüller et al., 2001; Shtyrov et al., 2012), it can be assumed that these word-specific MMNm changes indicate recovery of automatic language processing mechanisms in the left hemisphere.

Previous work showed that stimulus repetition effects usually lead to a reduction of the brain responses to words (Doyle et al., 1996), therefore, the observed enhancement is unlikely to reflect the repetition of words and pseudowords across pre- and post-testing sessions. Furthermore, the specificity of MMN enhancements to words but not pseudowords is a pattern distinct from that found in healthy subjects, where the reverse is typically found; frequent repetitions of pseudowords (but not words) leads to incremental MMN increases reflecting pseudowords learning (Shtyrov et al., 2010). Interestingly, left-hemispheric lateralisation of lexical MMN responses for words (relative to pseudowords) have been reported in previous studies with healthy individuals (Pulvermüller and Shtyrov, 2009; Shtyrov and Pulvermüller, 2007). In accordance with these previous data (for review see Shtyrov and Pulvermüller, 2007; Shtyrov, 2010), our results revealed strongly left-lateralised responses for words and pseudowords, with overall stronger signals for words than pseudowords in the typical MMN time window around 200 ms after stimulus recognition. Laterality quotient analysis of MMNm activation clearly indicated a shift to stronger LH-laterality following ILAT, also suggesting treatment-driven normalisation of physiological mechanisms underpinning lexical processing.

In this context, the left-hemispheric increase in word-specific MMNm in aphasia patients after therapy may constitute a neurophysiological marker of cortical reorganisation towards normal language processing. It also suggests that the MMNm could potentially be a neurophysiological correlate which is sensitive enough to detect changes in lexical processing even in patients with large cortical lesions. Thus, the current data support previous suggestions that MMN designs can be a valuable neurophysiological tool for clinical diagnosis and the mapping of treatment-related cortical changes (Näätänen et al., 2012; 2014).

MMNm activation enhancement over therapy is also in line with previous findings on ILAT- induced cortical changes. For example, in a MEG study using spoken word recognition, Breier et al. (2009) reported a left-hemispheric increase in brain activation over temporal areas following ILAT, which was found as late as three months after termination of the treatment. However, when the same patients were tested immediately after therapy, cortical changes were observed over the right hemisphere, indicating that lateralisation effects may be influenced by the specific recovery phase (Saur et al., 2006). Similarly, ultra-rapid activation changes (at latencies < 100 ms after spoken word onset) in the left hemisphere have been reported as a result of ILAT (MacGregor et al., 2015). Whereas left-hemispheric activation increase in perilesional areas was associated with clinical language improvements (Meinzer et al., 2008), other results revealed correlations of language skills with bilateral neurophysiological changes in the electroencephalogram (Pulvermüller et al., 2005). In line with our previous data (Pulvermüller et al., 2005), here, we found significant correlations between improvements in language comprehension, as measured by the Token Test, and word-evoked neuromagnetic changes in both cerebral hemispheres. However, our present findings suggest that the left hemisphere plays a more important role in cortical reorganisation when ‘automatic’ language processing is monitored in paradigms where participants are instructed to ignore language stimuli.

What are the possible neuronal mechanisms for a significant enhancement of left-hemispheric MMNm activation after successful therapy? A possible explanation could be based on Hebbian learning mechanisms (Hebb, 1949) occurring during the course of intensive learning and practising of pragmatic language use. As outlined in the introduction, ILAT is based on established neuroscientific principles, and these principles also provide a guideline for interpretation of the outcomes. One of those principles is *massed practice*, which is motivated by the Hebbian learning principle, that strengthening of synaptic connections between neurons results from frequent co-activation of neurons. Therefore, frequent and intensive practice of language skills could result in the formation of new lexical neuronal circuits or in strengthening of connections within the remains of word-related lexico-semantic circuits (Berthier and Pulvermüller, 2011). MEG measurements in general and our present data in particular do not allow for precise enough spatial localisation to decide between these possibilities. As in chronic PSA patients, large parts of the left-hemispheric fronto-temporal language system are impaired by brain lesions, perilesional areas may be primarily involved in re-establishing synaptic contacts within (partially) spared structural regions and lexico-semantic language circuits in both hemispheres. This mechanism of cortical reorganisation is consistent with observations of widespread cortical changes due to language therapy, suggesting the enlargement of these neuronal circuits and spreading over perilesional brain regions (and even homotopic right-hemisphere areas), depending on the language task patients are engaged with (see for example Meinzer et al., 2008; Mohr et al., 2014; Pulvermüller et al., 2005, Turkeltaub et al., 2011). The observed left (fronto-) temporal topography of the pre-post MMN change suggests neurophysiological changes, which may reflect better functionality of lexical semantic networks, which may be the basis for the observed improvement of language processing.

Why would the expansion and strengthening of lexical networks involve primarily areas in the left hemisphere and, to a lesser extent, areas in the right hemisphere? On a theoretical

level, changes in both hemispheres would have been expected as intensive practise of pragmatic communication most likely involves brain areas in both hemispheres. The fact, that we found correlations between language improvements in the TT and enhanced MMNm activity after therapy in both hemispheres indicates that changes in the left and right hemisphere indeed occurred over the course of the treatment. However, the significant word-specific enhancement of neurophysiological activity after therapy occurred only in the LH. It may be possible that therapy-related changes in functional lateralisation strongly depend on factors such as stimulus characteristics, task demands or on the neuroimaging method applied (Crosson, 2005; Mohr et al., 2014). Even in healthy individuals, differences in linguistic tasks or stimuli (for example, lexical versus syntactic properties) lead to differences in functional lateralisation patterns (Mohr et al., 1994; 2007; Pulvermüller et al., 2009). The present study used a passive listening MMN paradigm with common mono-syllabic English words, a task which does not require active attention or any behavioural responses from participants. As this MMN paradigm measures automatic language processing, it may have required too few processing demands to draw upon any putative right-hemispheric lexico-semantic circuits.

Moreover, the observed left-hemispheric bias of therapy-induced changes in the present study could be the consequence of left-hemispheric lateralisation of MMN generators: although the auditory MMNm seems to be generated in frontal areas in both hemispheres (Alho, 1995), it has been suggested that there is a left-hemispheric bias for language related MMN generators (Näätänen et al., 1997). It has also been noted that, depending on specific features of words, and especially aspects of their meaning, laterality patterns may substantially differ across word categories (Pulvermüller et al., 2004; 2009). In previous studies, bilateral neurophysiological changes across ILAT in chronic aphasia have been found in EEG recordings and distributed source localisation when patients performed linguistic tasks requiring active behavioural

responses, such as lexical decisions (Pulvermüller et al., 2005), naming (Kurland et al., 2012), or attention to semantic content, as for example in silent attentive reading (Barbancho et al., 2015).

In contrast to our findings, functional recruitment of fronto-temporal areas within the unaffected right hemisphere (homotopic to left-hemispheric language areas) after ILAT have been observed in studies requiring attention and complex semantic differentiation, for example when sentences with high and low semantic ambiguity are presented (Mohr et al., 2014). Other studies also favour a significant role of the non-dominant right hemisphere in the functional recovery of language (Richter et al., 2008; Teki et al., 2013). On the other hand, while many authors postulate a significant contribution of the right hemisphere in functional language recovery of aphasia (Berthier and Pulvermüller, 2011; Crosson et al., 2005), some authors have suggested that an increase of right hemispheric activity in language tasks may be an index of (or even be causal for) inefficient language processing and therefore may not be helpful for language recovery (e.g. Heiss and Thiel, 2006).

Source localisation analysis might have provided additional information on the specific cortical localisation of neuromagnetic changes after therapy. State-of-the art distributed source analysis requires high-quality structural MR images, particularly when applied to pathologically modified brain tissue. As a large proportion of our patients were unable to undergo MR scanning due to associated health risks, it was not possible to obtain sufficient structural MR scans to perform this analysis. Furthermore, it should be noted that signal-space analysis is a more straightforward quantification technique, which only involved simple arithmetic operations on recorded signals, unchanged by non-unique and often non-linear operations used in inverse problem solution techniques. It therefore may be more practical for (future routine) clinical use on patients with variable lesions who may not have structural MR-based conductor volume models. Importantly, the positive correlation between ERFs and clinical symptom improvements are of translational relevance.

A potential compromise between signal-space and distributed source analyses could be the so-called equivalent current dipole (ECD) technique, often used to approximate the overall activity of cortical patch without making any strong conclusions of its exact distribution or size. However, the ECD approach could bring in other caveats, as it assumes a single source ('dipole'), which most likely is not the physiological basis for complex language-related neural activity (Dale et al., 2000; Pulvermüller et al., 2003; MacGregor et al., 2012), particularly in a potentially quite underdetermined situation of functional recovery. As the neural activity is reorganized in the damaged tissue, it is not known what shape this reorganization takes, and one possible outcome of a lesion is the fragmentation of activity. The resulting fragments of both retained and compensatory neural activations may not necessarily be spatially aligned, which would problematic for a point-like ECD estimate.

Nevertheless, we suggest that future studies, provided they could obtain high-quality conductor-volume models of individual brains, should evaluate various source analysis techniques for use in paradigms similar to that applied here, as well as aim at employing sophisticated distributed source reconstruction techniques that could track in more detail of the neuroanatomical bases of the recovery processes documented here in signal space. Consistent with our present data, some previous attempts at distributed source analysis in aphasic patients undergoing language therapy (Pulvermüller et al., 2005) suggested that source changes in both cortical hemispheres correlate with clinical language improvements.

In future research, it would be important to systematically investigate functional language recovery in fully controlled randomised trials with both, therapy and control groups using fine grained source localisation performed on a subject by subject basis. Furthermore, neuronal changes during different phases of recovery from PSA and the impact of language therapy on clinical (language) changes during these recovery stages will be of major interest.

5. Conclusions

Patients with chronic post stroke aphasia showed significant improvements in language functions and everyday communication after two weeks of intensive language action therapy. Improved language comprehension was correlated with neurophysiological changes in both cerebral hemispheres. Following two weeks of treatment, increased neuromagnetic activation patterns in the MMNm emerged around 200 ms after the stimulus recognition point. This post-therapy activation enhancement was specific to words and was visible over the left hemisphere, which indicates a major contribution of left-hemispheric perilesional regions in re-establishing language networks in the cortex. Correlations between improvements on language tests related to therapy and the enhancement of MMN responses were seen for both left- and right-hemispheric recordings, indicating some contribution of the RH to therapy success as well. Methodologically, the results show how the passive lexical MMN paradigm can be usefully used as a tool for mapping language recovery and therapy-induced neuroplasticity after stroke.

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Figure captions

Figure 1: Waveforms of the standard and deviant stimuli with respective stimulus duration and phonetic representations time locked to MEG/ERFs.

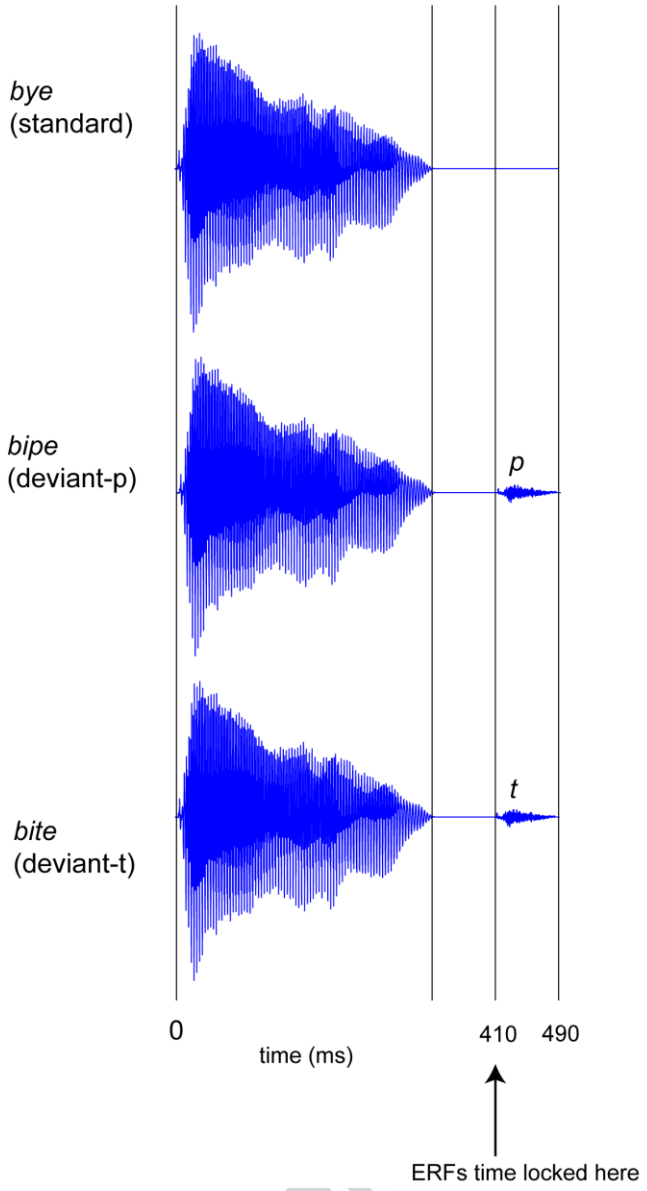
Figure 2. Event-related magnetic field gradients (n=12) elicited in response to the standard and deviant stimuli (words and pseudowords) for pre- and post-therapy sessions. Data are averaged over the fronto-temporal gradiometer pairs (left and right hemispheres) included in the analyses. The MMNm time window (170-210 ms) in which significant changes in activation were observed is highlighted.

Figure 3. Bar chart showing the significant *Lexicality x Hemisphere x Session* interaction in the event-related magnetic field gradients in the MMN (170-210 ms) time window. Asterisks indicate significant differences between conditions.

Figure 4. Event-related magnetic field gradients of the MMNm responses (deviants minus standards) for pre- versus post-therapy session for words and pseudowords for a typical left temporal gradiometer pair (0212) and its right hemispheric homologue (1322). The time window 170-210 ms is highlighted in red.

Figure 5. Topographical field gradient maps showing distribution of the MMNm responses to words for the pre- and post-therapy session over the left and right hemisphere. Analyses were based on mean responses over the 170-210 ms time window where the significant three-way-interaction was observed.

Figure 6. Scatterplot showing significant correlations between language improvement (in the Token Test, TT) and MEG activity after therapy. In the left hemisphere (LH), a word-specific increase of brain activation correlates with a decrease of error rates in the TT. In the right hemisphere (RH), decreased error rates correlate with reduced brain activation to words after therapy.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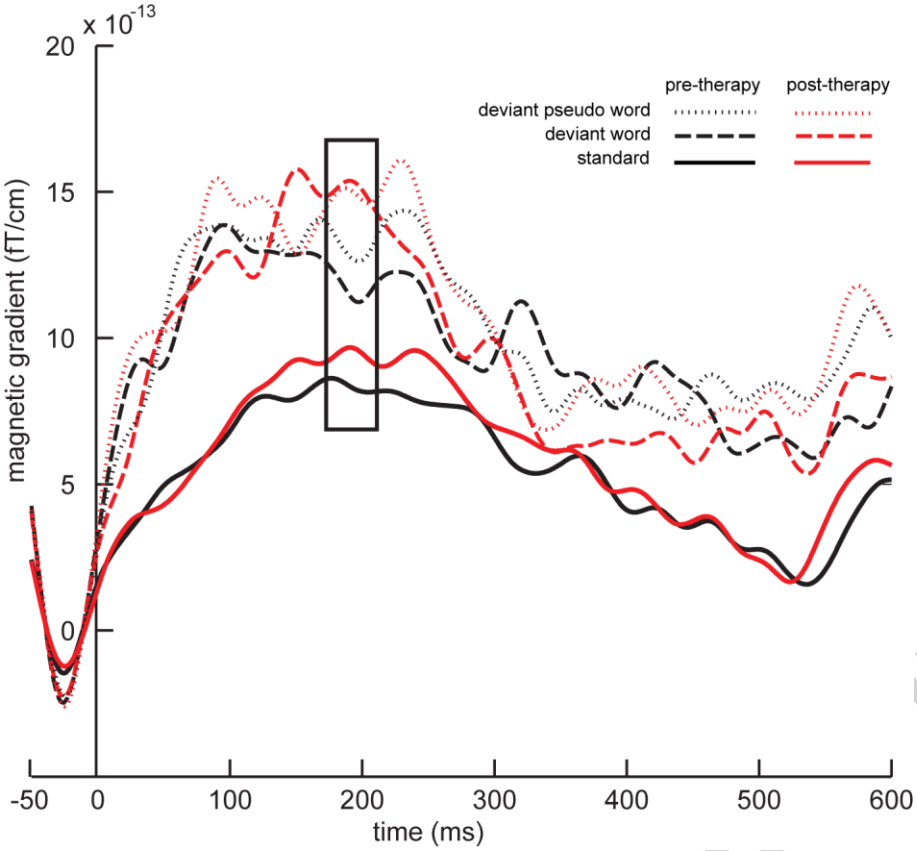

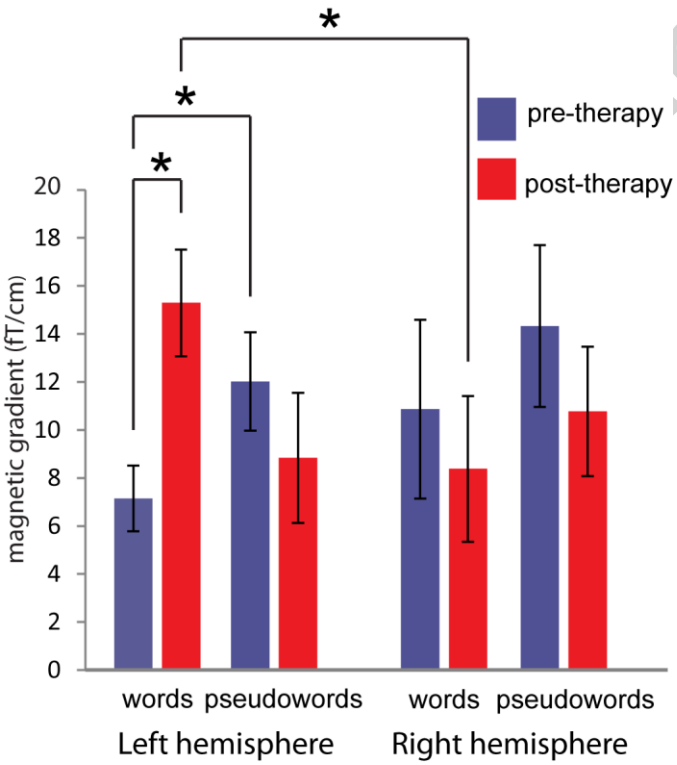

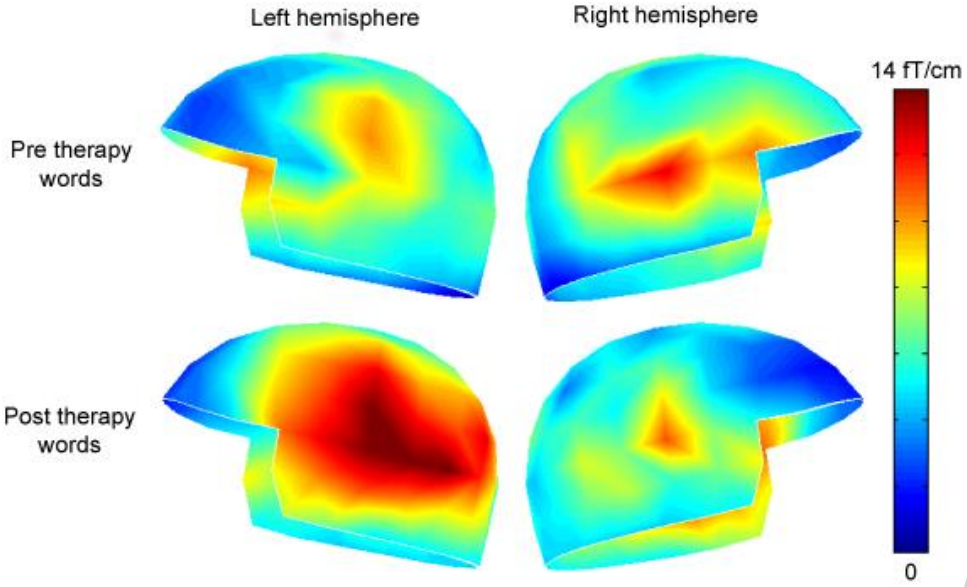

- Changes in spatio-temporal MEG activation before and after intensive language action therapy (ILAT) were measured in patients with chronic post stroke aphasia.
- Patients showed clinical language improvements that correlated with increased mismatch negativity (MMN) responses after ILAT.
- Post-therapy cortical activation enhancement occurred specifically for words in the left hemisphere.
- Perilesional regions in the left hemisphere contribute to language restitution and neuroplasticity after stroke.